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Ring Opening of 4′,5′-Epoxynucleosides: A Novel Stereoselective Entry to 4′-*C*-Branched Nucleosides

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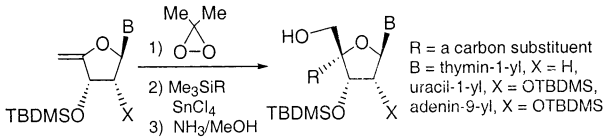
ABSTRACT



Stereoselective synthesis of 4′-α-carbon-substituted nucleosides has been accomplished through epoxidation of 4′,5′-unsaturated nucleosides with dimethyldioxirane (DMDO) and successive $SnCl_4$-promoted ring opening of the resulting 4′,5′-epoxynucleosides with organosilicon reagents.

Nucleoside analogues are recognized as an important class of biologically active compounds, especially as antiviral and antitumor agents.[1] Recently, 4′-substituted nucleosides have attracted much attention because of the discovery of the potent anti-HIV agents 4′-azido- (**1**) and 4′-cyanothymidine (**2**).[2] Although incorporation of heteroatoms into the 4′-position of nucleosides can be carried out by the simple electrophilic addition to 4′,5′-unsaturated nucleosides,[2,3] this method is not suitable for carbon substituents.

The most commonly utilized method for the preparation of 4′-branched analogues is manipulation of 4′-hydroxymethyl derivatives of nucleosides or sugars prepared via an aldol-Cannizzaro reaction of the corresponding aldehyde.[4,5] Other recently reported methods include intramolecular radical cyclization of a 3′-*O*-silicon-tethered nucleoside C4′-radical[6] and electrophilic substitution of nucleoside 5′-esters.[7]

Although ring opening of epoxides with carbon nucleophiles constitutes a powerful synthetic operation for C−C bond-forming reactions,[8] little attention has been paid for its application to the synthesis of branched sugar-nucleosides.[9] In this paper, we wish to describe a novel method for the stereoselective synthesis of 4′-α-carbon-substituted nucleosides based on epoxidation of 4′,5′-unsaturated nucleosides followed by $SnCl_4$-assisted ring opening with organosilicon reagents.

One would readily anticipate from their enol ether structure that 4′,5′-unsaturated nucleosides would be highly susceptible to nucleophilic attack under acidic conditions. In fact, it has

(1) For a review, see: *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

(2) Prisbe, E. J.; Maag, H.; Verheyden, J. P. H.; Rydzewski, R. M. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 101−113.

(3) (a) Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc*. **1976**, *98*, 3346−3357. (b) Owen, G. R.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem*. **1976**, *41*, 3010−3017. (c) Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc*. **1975**, *97*, 4386-4395. (d) Sasaki, T.; Minamoto, K.; Kuroyanagi, S.; Hattori, K. *Tetrahedron Lett*. **1973**, *14*, 2731−2733. (e) Sasaki, T.; Minamoto, K.; Hattori, K. *J. Am. Chem. Soc.* **1973**, *95*, 1350−1351.

(4) (a) Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. *J. Med. Chem.* **1999**, *42*, 2901−2908. (b) Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem*. **2000**, *43*, 4516−4525.

(5) Other synthetic methods: (a) Secrist, J. A, III; Winter, W. J., Jr. *J. Am Chem. Soc*. **1978**, *100*, 2554−2555. (b) Haraguchi, K.; Tanaka, H.; Itoh, Y.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem*. **1996**, *61*, 851−858.

(6) Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem*. **1999**, *64*, 7153−7157.

(7) Jung, M. E.; Toyota, A. *J. Org. Chem*. **2001**, *66*, 2624−2635.

(8) For a review, see: Smith, J. G. *Synthesis* **1984**, 629−656.

(9) Ashwell, M.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res*. **1987**, *15*, 2157−2166.

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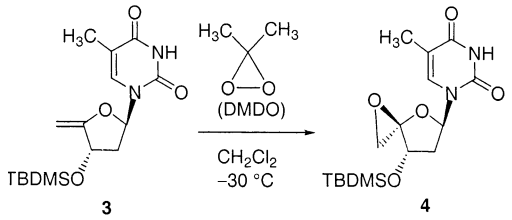
been reported that *m*-CPBA-oxidation of 4′,5′-unsaturated thymidine (4′,5′-didehydro-5′-deoxythymidine) in MeOH resulted in the formation of 4′-methoxythymidine as a mixture of 4′-epimers.[2,10] We, therefore, examined dimethyldioxirane (DMDO), which can be used under neutral conditions in aprotic solvents.[11] When 3′-*O*-TBDMS-4′,5′-unsaturated thymidine (**3**) was treated with an acetone solution of DMDO (1.5 equiv) in CH_2Cl_2 at −30 °C, the reaction went to completion within 0.5 h and 4′,5′-epoxythymidine **4** (a single isomer, evidenced by ^{1}H NMR) was obtained simply by removal of the solvents (Scheme 1). The

Scheme 1

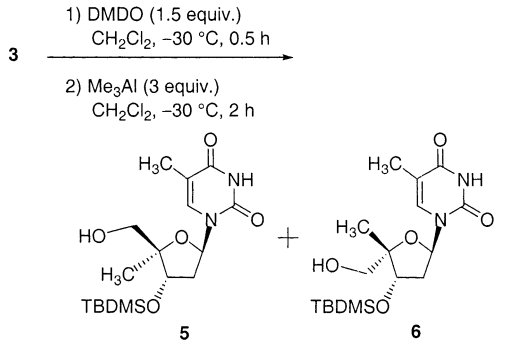


3 **4**

depicted stereochemistry of **4** came from the observed nOe correlation between H-5′/Si-*t-Bu* (0.9%) as well as the assumption that the α-face of the 4′,5′-double bond would be shielded by the TBDMS group. Although DMDO has been known to oxidize the pyrimidine base of nucleosides,[12] no such side reaction was observed in the epoxidation of **3**.

The initial attempt to ring-open **4** was carried out with Me_3Al (3 equiv) as shown in Scheme 2. Although exclusive

Scheme 2



5 **6**

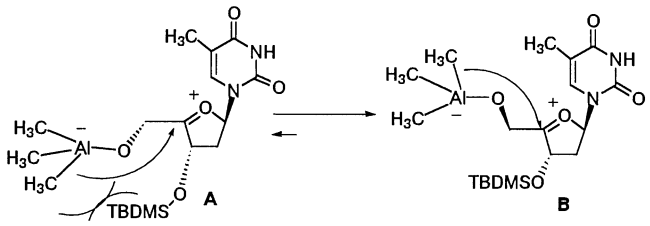
cleavage of the oxirane ring at the 4′-position was seen, the stereochemical outcome of this reaction was discouraging, forming the 4′-*β*-methyl isomer **6** (64%) as the major product together with **5** (5%). The stereochemistry of these products

(10) Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crawford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440−1451.

(11) (a) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227−232. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(12) Example of oxidative modification of pyrimidine base with DMDO: Saladino, R.; Bernini, R.; Crestini, C.; Minocione, E.; Bergamini, A.; Marini, S.; Palamara, A. T. *Tetrahedron* **1995**, *51*, 7561−7578.

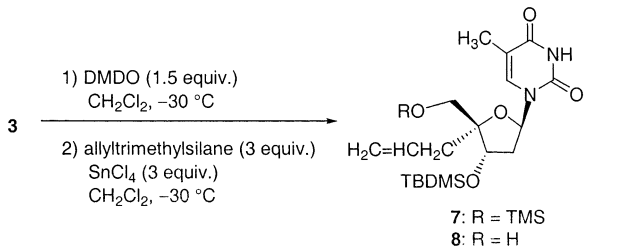
Scheme 3



was determined by nOe experiment: **5** H-1′/Me-4′ (4%), **6** H-3′/Me-4′ (9%), and H-6/Me-4′ (3%). As shown in Scheme 3, the result can be rationalized by assuming that the oxonium intermediate is in equilibrium as the conformers **A** and **B**, and that "intramolecular" methyl transfer to the 4′-position had occurred predominantly from **B** due to the steric repulsion associated with **A**. This assumption led us to examine Lewis acid-mediated intermolecular ring opening of **4** with organosilicon reagents.

Reaction of **4** with allyltrimethylsilane (3 equiv) using $SnCl_4$ (3 equiv) gave two products (Scheme 4). Their ^{1}H

Scheme 4



NMR spectra showed that the more polar product was the expected 4′-α-allylthymidine **8** [nOe data: H-5′/H-3′ (5.3%) and H-1′/CH_2═CHCH_2-4′ (0.8%)] while the less polar one was its 5′-*O*-trimethylsilyl derivative (**7**). Thus, simple extractive workup of the reaction mixture followed by treatment with NH_3/MeOH enabled the isolation of **8** in 80% yield. The use of other Lewis acids, such as $TiCl_4$ or $EtAlCl_2$, gave mainly thymine, and **8** was obtained only in very low yields (5−7%).

The above $SnCl_4$-assisted stereoselective allylation also worked with 4′,5′-epoxides derived from **9** and **13** (Figure

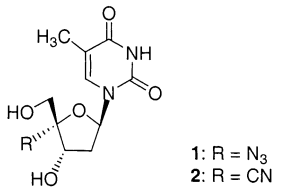


Figure 1.

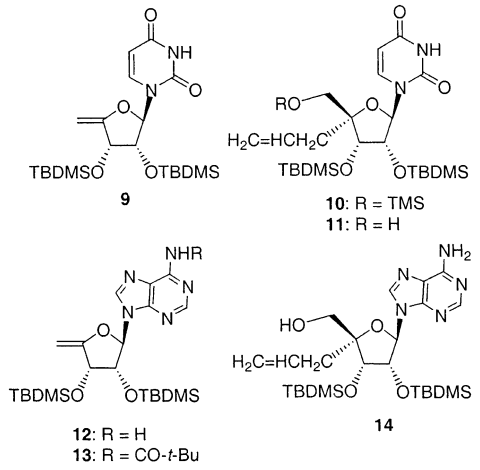
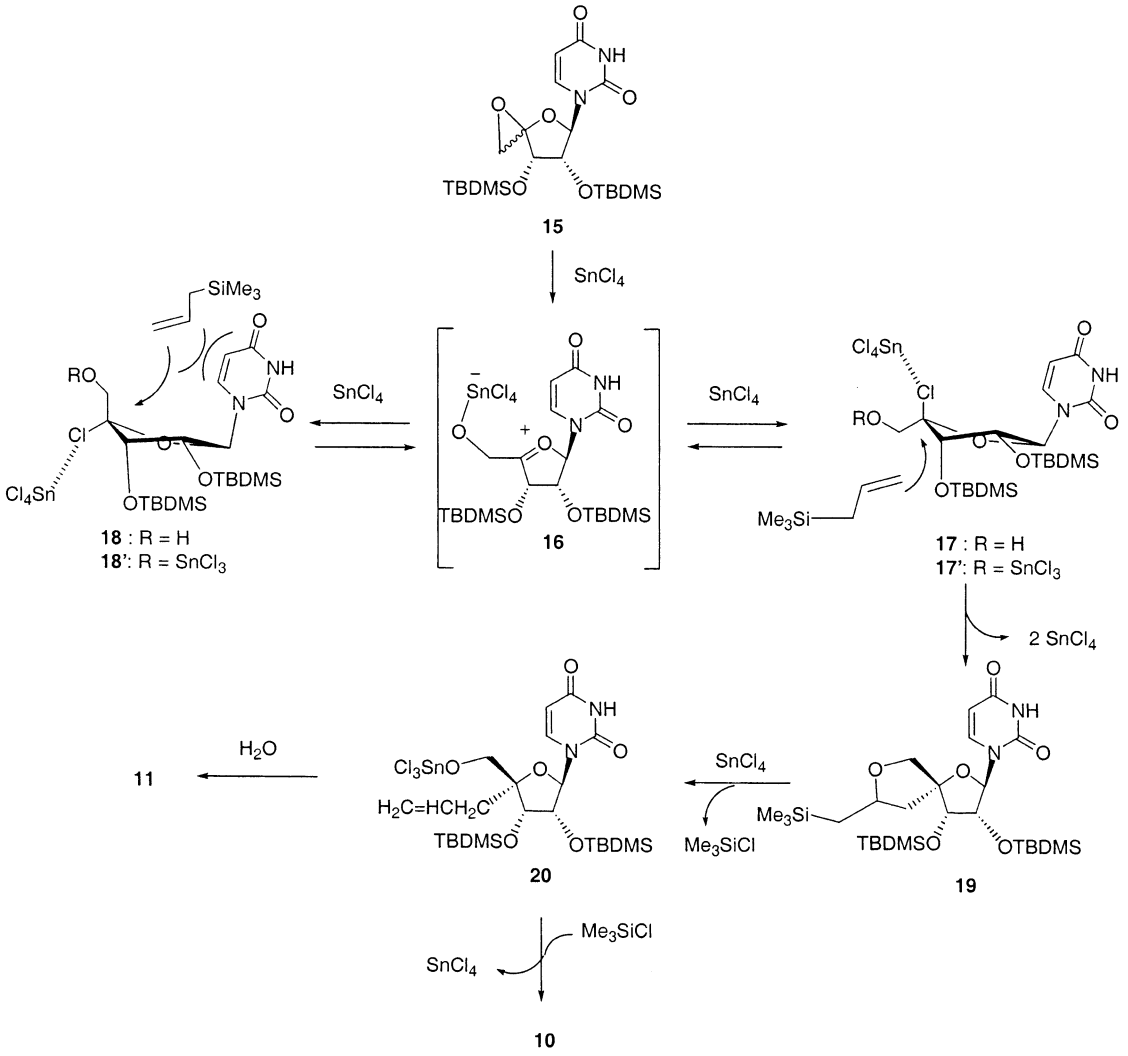


Figure 2.

2). Thus, allylation of the epoxide prepared from **9** gave a mixture of **10** and **11**. After NH_3/MeOH treatment of the mixture, 4′-α-allyluridine **11** was isolated in 90% overall yield from **9**. In the case of **12**, to avoid N^1-oxidation with DMDO, it was necessary to acylate the 6-NH_2 group. By using the N^6-pivaloyl derivative **13**, 4′-α-allyladenosine **14** was obtained in 52% overall yield.

To elucidate the mechanism of the present allylation, the above-mentioned reactions of **9** were studied in some detail. Epoxidation of **9** with DMDO gave a 4′,5′-epoxide **15** as a single isomer, although its stereochemistry could not be determined with an nOe experiment. When this epoxide was reacted solely with $SnCl_4$ in CH_2Cl_2, two 4′-chlorinated products (**17** and **18**) were isolated. The stereochemistry was established on the basis of an nOe experiment. Analysis of their $J_{1',2'}$ and $J_{2',3'}$ values suggested that **17** and **18** would take the conformations as shown in Scheme 5, respectively. Independent treatment of **17** and **18** again with $SnCl_4$ resulted in isomerization, forming both compounds. Although no reaction took place by adding allyltrimethylsilane to a CH_2Cl_2 solution of **17**, addition of a catalytic amount of $SnCl_4$ (0.5 equiv) to this mixture caused an instantaneous reaction to give the spiro intermediate **19** (a mixture of two

Scheme 5



diastereomers) that was isolated by HPLC and fully characterized. In the reaction medium, **19** was found to be converted slowly to **10** and **11**. Compound **18** behaved exactly in the same manner as **17**. These observations led us to propose the reaction mechanism in Scheme 5. The 4′-β- (**17′**) and 4′-α-chloro (**18′**) derivatives exist in equilibrium, and are interconvertible through the oxonium ion **16**. For the $SnCl_4$-assisted reaction with allyltrimethylsilane, **18′** would be kinetically less favored because of the pseudoequatorial orientation of the chlorine atom,[13] and presumably also due to steric hindrance exerted by the base moiety. On the other hand, the pseudoaxial chlorine atom in **17′** as well as the sterically less encumbered α-face permit its ready S_N2 reaction with allyltrimethylsilane to lead to the intermediate **19**. The β-effect of the silicon atom ensures regioselective opening of the spiro ring to yield **20**. Trapping of **20** with TMSCl gives rise to **10**, whereas quenching with H_2O furnishes **11**.

Finally, the scope of the present reaction was briefly examined by reacting 4′,5′-epoxythymidine derivative **4** with other organosilicon reagents (Figure 3). Compounds **21** (47%) and **22** (32%) were synthesized as a single isomer by using (2-bromoallyl)trimethylsilane and (cyclopentenyl)-trimethylsilane, respectively, in CH_2Cl_2 in the presence of $SnCl_4$ (3 equiv). It would be worthy to mention that the present method provides an access to a potent anti-HIV agent, 4′-α-cyanothymidine, since a cyano group can be introduced into the 4′-position by using cyanotrimethylsilane to yield **23** (45%).

(13) Eliel, E. L.; Ro, R. S. *Chem. Ind.* **1956**, 251−252.

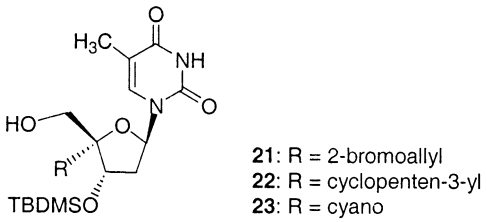


Figure 3.

In conclusion, a novel method for the stereoselective synthesis of 4′-α-carbon-substituted nucleoside analogues has been disclosed, using the $SnCl_4$-assisted ring opening of 4′,5′-epoxynucleosides with organosilicon reagents. The evidence-based reaction mechanism of 4′-α-selective allylation has also been proposed through the present study.

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Supporting Information Available: Experimental procedures and full characterization for compounds **3**, **5**, **6**, **8**−**14**, **17**−**19**, and **21**−**23**; ^{1}H NMR and MS spectrum of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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